

## Learning Objectives

1. Accurately diagnose asthma and assess severity, taking into account the heterogeneous disease state, in order to improve patient health outcomes and reduce the high burden of disease
2. Select effective pharmacotherapy regimens based on disease severity, sub-type, phenotype, or endotype and use a stepwise approach for long-term control and management of asthma
3. Review asthma self-management including proper inhaler use and technique to ensure correct delivery of medication and improved health outcomes

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## Outline

- ▶ Impact and Pathophysiology
- ▶ Diagnosis and Assessment
- ▶ Management
  - Goals of Management
  - Non-pharmacologic and Pharmacologic Strategies
  - Approach to Poorly Controlled Asthma
  - Novel Targets of Therapy for Severe Asthma
- ▶ Take Home Messages

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## What is Asthma?

- ▶ A **common** and **complex** disease
- ▶ **Chronic** inflammation of the airways
- ▶ **Heterogeneous** nature

### Characterized by:

Variable and recurrent symptoms

Airflow obstruction

Bronchial hyperresponsiveness

Underlying inflammation

Martinez FD, et al. Asthma. Lancet. 2006 Volume 382, No. 9901, p1360–1372.

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## Burden of Disease

- ▶ Asthma affects adults and children of all ages
- ▶ Over 26 million Americans are diagnosed with asthma
- ▶ Prevalence is increasing approx. 2.9% per year
- ▶ Increases are observed among all demographic groups
- ▶ Higher rates of asthma prevalence among women and some minority populations

Akinbami LJ et al. National Center for Health Statistics. 2012; Croissant S. Adv Exp Med Biol. 2014; 795:17-29; Moorman JE, Akinbami LJ, Bailey CM, et al. National Surveillance of Asthma in the United States, 2001-2010. National Center for Health Statistics. Vital Health Stat 3(35); 2012.

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## Burden to Society in US



Asthma-related health expenditure in the US amounted to approximately **\$80 billion** in 2013



**13.8 million** missed days of school yearly



Nearly **1 in 3** adults miss at least one day of work because of their asthma

Nurmagambetov T, et al. Annals ATS. 2018; CDC. MMWR 2011;60:547–52; CDC. Asthma Statistics Fact Sheet. [www.cdc.gov/asthma/asthma\\_stats/astStatChild\\_Missed\\_School\\_Days.pdf](http://www.cdc.gov/asthma/asthma_stats/astStatChild_Missed_School_Days.pdf); CDC. Asthma Fact Sheet. [https://www.cdc.gov/asthma/impacts\\_nation/AsthmaFactSheet.pdf](https://www.cdc.gov/asthma/impacts_nation/AsthmaFactSheet.pdf)

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## Asthma in 2018

### Multiple Unmet Medical Needs

Although national and international guidelines for asthma control have been established, current standard-of-care has yet to meet them<sup>1,2</sup>

5–10% of patients have severe asthma,<sup>3</sup> and severe asthma often fails to respond to conventional therapy<sup>4,5</sup>

Large number of hospitalizations for people with severe asthma every year

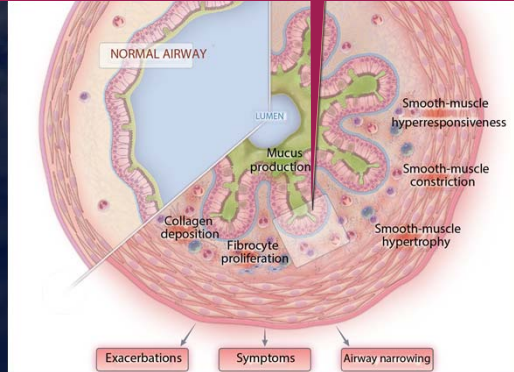
Uncontrolled asthma is associated with significant morbidity and mortality and a high economic burden<sup>6</sup>

1. Bateman ED, et al. Am J Respir Crit Care Med. 2004;170:836–44; 2. Bateman ED, et al. Eur Respir J. 2007;29:56–62  
3. Chung KF, et al. Eur Respir J. 2014;43:343–73; 4. Holgate ST, Polosa R. Lancet. 2006;368:780–93  
5. Partridge MR. Eur Respir Rev. 2007;16:67–72; 6. Chipps BE, et al. J Allergy Clin Immunol. 2012;130:332–42

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## Pathophysiology

Hyperresponsiveness, remodeling, mucus production, and smooth-muscle constriction and hypertrophy

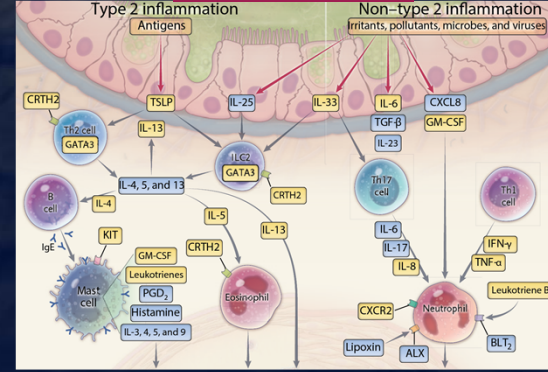


Israel E, et al. N Engl J Med. 2017; 377(10):965–76.

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## Pathophysiology

### Multiple Cells and Mediators



Israel E, et al. N Engl J Med. 2017; 377(10):965–76.

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Meet Katie: 30-Year-Old Female

cases

A new patient presents to your practice. She is a 30-year-old woman who 3-4 years ago developed rhinitis and nasal congestion, diagnosed as chronic rhinosinusitis with nasal polyps.

She has never been diagnosed with asthma, but says that every night for the past six months she has been experiencing “wheezing attacks” where she feels like her chest is tightening up.

**How would you establish a diagnosis of asthma for this patient?**

# Establishing the Correct Diagnosis

## Characteristic history

- episodic symptoms
- characteristic triggers
- characteristic response to medications

## Characteristic examination

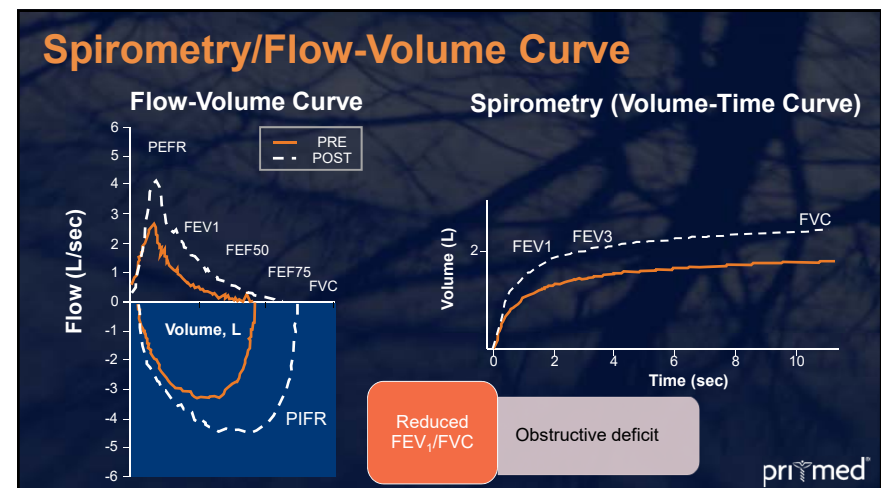
- diffuse musical expiratory wheezes

## Diagnostic testing

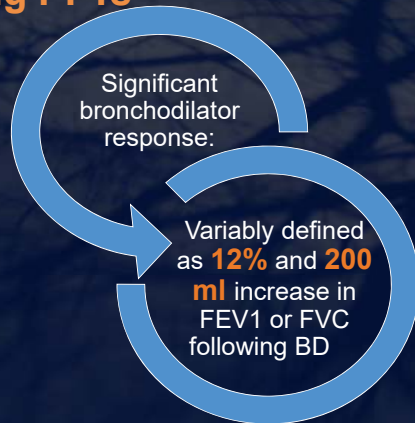
# Pulmonary Function Testing

## Variable expiratory airflow obstruction

- Varies over time
- Improves following bronchodilator
- Can be induced by provocative stimuli
  - e.g., methacholine



## Interpreting PFTs



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## Misdiagnoses Among Asthma and Other Respiratory Conditions Are Common

≈ 30% of adults with respiratory diseases have been misdiagnosed with asthma

Age	6 – 11 years	12 – 39 years	40+ years
Conditions	<ul style="list-style-type: none"> <li>Chronic upper airway cough syndrome</li> <li>Inhaled foreign body</li> <li>Bronchiectasis</li> <li>Primary ciliary dyskinesia</li> <li>Congenital heart disease</li> <li>Bronchopulmonary dysplasia</li> <li>Cystic fibrosis</li> </ul>	<ul style="list-style-type: none"> <li>Chronic upper airway cough syndrome</li> <li>Vocal cord dysfunction</li> <li>Hyperventilation, dysfunctional breathing</li> <li>Bronchiectasis</li> <li>Cystic fibrosis</li> <li>Congenital heart disease</li> <li>Alpha<sub>1</sub>-antitrypsin deficiency</li> <li>Inhaled foreign body</li> </ul>	<ul style="list-style-type: none"> <li>Vocal cord dysfunction</li> <li>Hyperventilation, dysfunctional breathing</li> <li>COPD</li> <li>Bronchiectasis</li> <li>Cardiac failure</li> <li>Medication-related cough</li> <li>Parenchymal lung disease</li> <li>Pulmonary embolism</li> <li>Central airway obstruction</li> </ul>

COPD = chronic obstructive pulmonary disease.  
 Aaron SD, et al. JAMA. 2017; 317(3):269-279; 2018 GINA report, global strategy for asthma management and prevention. <http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed 2018 May 7.

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Katie Revisited: 30-Year-Old Female

cases

You performed spirometry.

Katie's FEV1 is less than 65% of predicted, increasing by 15% following bronchodilator.

How would you assess the severity of her asthma?

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## Assessing Asthma Severity & Control

### Current impairment

- Symptoms (daytime, nighttime, and frequency of use of rescue bronchodilator)
- Exercise limitation
- Lung function

### Future risk

- More than 1 oral steroid course in last year

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## Classifying Asthma Severity: NAEPP

Components of Severity		Classification of Asthma Severity (Youths ≥12 of Age and adults)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	<2×/month	3-4×/month	>1×/week but not nightly	Often 7×/week
	SABA use for symptom control	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	<ul style="list-style-type: none"><li>● Normal FEV<sub>1</sub> between exacerbations</li><li>● FEV<sub>1</sub> &gt;80% predicted</li><li>● FEV<sub>1</sub>/FVC normal</li></ul>	<ul style="list-style-type: none"><li>● FEV<sub>1</sub> &gt;80% predicted</li><li>● FEV<sub>1</sub>/FVC normal</li></ul>	<ul style="list-style-type: none"><li>● FEV<sub>1</sub> &gt;60% but &lt;80% Predicted</li><li>● FEV<sub>1</sub>/FVC reduced 5%</li></ul>	<ul style="list-style-type: none"><li>● FEV<sub>1</sub> &lt;60% predicted</li><li>● FEV<sub>1</sub>/FVC reduced &gt;5%</li></ul>
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/yr	→		
		Consider severity and interval since last exacerbation; frequency and severity may fluctuate over time for patients in any severity category			
		Relative annual risk of exacerbations may be related to FEV <sub>1</sub>			

NHLBI. National Asthma Education and Prevention Program. Expert Panel Report 3: page 115. Available at: <http://www.nhlbi.nih.gov/guidelines/index.htm>.

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## Assessing Asthma Control

- ▶ The goal of all asthma therapy is to **ACHIEVE CONTROL**
- ▶ Focus of treatment
  - ▶ Airway inflammation
- ▶ Good control impacts future risk of exacerbation

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## Assessing Asthma Control: NAEPP

Components of Severity		Classification of Asthma Control (Youths ≥12 years of age & adults)		
		Well-Controlled	Not Well-Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2/month	1-3/month	≥4/week
	SABA use for symptom control	≤2 days/week	>2 days/week	Several times per day
	Interference with normal activity	None	Some limitation	Extremely limited
	FEV <sub>1</sub> or peak flow	>80% pred/personal best	60-80% pred/personal best	<60% pred/personal best
	Validated questionnaires			
Risk	ATAQ	0	1-2	3-4
	ACQ	≤0.75	≥1.5	N/A
	ACT	≥20	16-19	≤15
	Exacerbations	0-1 per year	2-3 per year	>3 per year
Risk	Reduction in lung growth	Evaluation requires long-term follow-up care.		
	Treatment-related adverse effects	Medication side effects vary in intensity from none to very troublesome. Level of intensity does not correlate to specific levels of control but should be considered in overall assessment of risk.		

NHLBI. National Asthma Education and Prevention Program. Expert Panel Report 3: page 118. Available at: <http://www.nhlbi.nih.gov/guidelines/index.htm>.

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## Modified Version: Asthma Control

	Well Controlled	Not Well Controlled	Very Poorly Controlled
Short Acting Beta Agonist Use	<2 days/week	>2 days/week	Several times a day
Exacerbations needing oral corticosteroids	0-1/year	≥ 2/year	
Asthma Control Test (ACT) Score	≥20	16-19	≤ 15

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## Asthma Control Test

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

All of the time (1) Most of the time (2) Some of the time (3) A little of the time (4) None of the time (5)

2. During the past 4 weeks, how often have you had shortness of breath?

More than once a day (1) Once a day (2) 3 to 5 times a week (3) Once or twice a week (4) Not at all (5)

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week (1) 2 or 3 nights a week (2) Once a week (3) Once or twice a week (4) Not at all (5)

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day (1) 1 or 2 times per day (2) 2 or 3 times per week (3) Once a week or less (4) Not at all (5)

5. How would you rate your asthma control during the past 4 weeks?

Not controlled at all (1) Poorly controlled (2) Somewhat controlled (3) Well controlled (4) Completely controlled (5)

**Well-controlled asthma:  $\geq 20$**

Copyright 2002, by Sanofi-Schering-Plough  
Asthma Control Test is a trademark of Sanofi-Schering-Plough

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## Our Understanding of Asthma is Changing

### Previous Approach

- Patients with similar observable clinical characteristics have been grouped and treated similarly

### The Challenge

- Many patients may not respond or be controlled on therapy considered to be the standard of care

**“One size doesn’t fit all”**

### Evolving Understanding

- Clinical differences in treatment response are related to underlying variations in multiple mechanisms

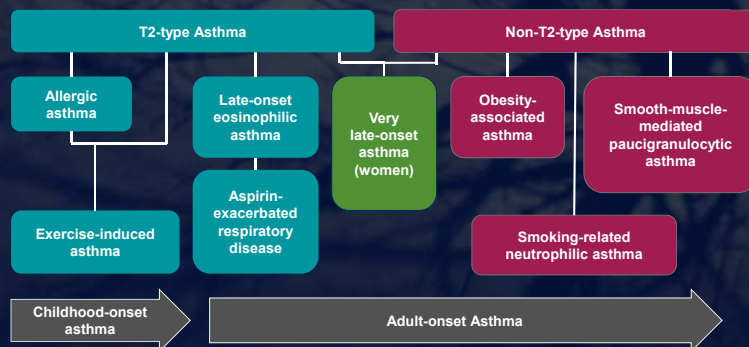
- genetic
- pharmacologic
- physiologic
- biologic
- immunologic

The heterogeneity in treatment response has inspired discussion of a precision approach to care that tailors treatment to the patient

Muraro A, et al. J Allergy Clin Immunol. 2016;137(5):1347–1358

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## Emerging Asthma Phenotypes



Holgate ST, et al. Nat Rev Dis Primers. 2015;1:15025

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## Focus is Shifting Toward the Identification of Disease Mechanisms

What can be observed and measured clinically?

**Observable Characteristics (Phenotype)**

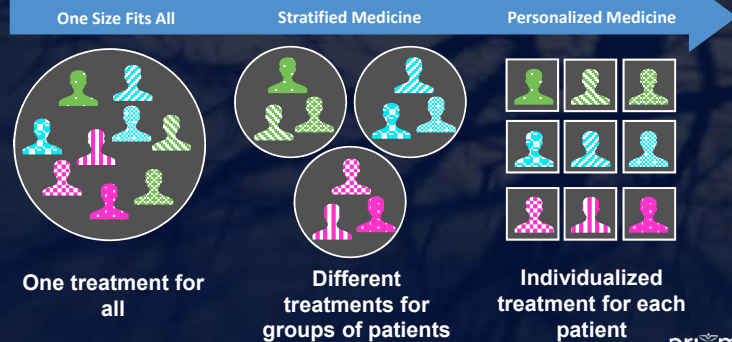
What are the potential drivers of disease?

**Pathophysiological Mechanism (Endotype)**

Lotvall J, et al. J Allergy Clin Immunol. 2011;127(2):355-360.

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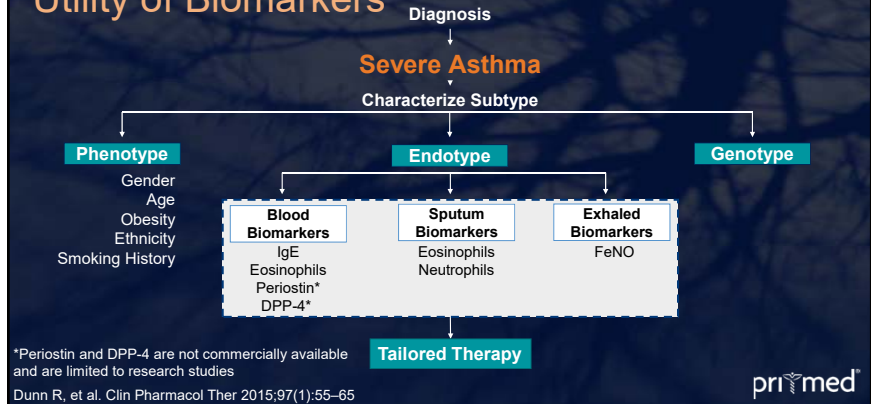
## Understanding Disease Mechanisms May Guide Decisions to Personalized Approach



Willis JC, Lord GM. Nat Rev Immunol. 2015;15:323-329.

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## Personalized Approach to Asthma Utility of Biomarkers



\*Periostin and DPP-4 are not commercially available and are limited to research studies

Dunn R, et al. Clin Pharmacol Ther 2015;97(1):55-65

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## Comparison of Asthma Biomarkers

	Suggested Cut-Off Values	Advantages	Limitations
FeNO	> 50 ppb	Simple, non-invasive test	Affected by age, height, sex, smoking, and respiratory infections
Blood eosinophils	> 150 vs > 300 vs > 400 cells/ $\mu$ L	Simple blood test	Affected by allergen exposure, steroids, and infection
Sputum eosinophils	$\geq 3\%$	Good correlation with type 2 asthma	Semi-invasive; confined to research settings

ppb = parts per billion.  
Parulekar AD, et al. Curr Opin Pulm Med. 2016;22(1):59-68.

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Katie Revisited: 30-Year-Old Female

cases

Begun on an inhaled steroid (fluticasone propionate 110 two puffs twice daily) and a rescue bronchodilator (albuterol) to be taken up to 4 times daily as needed.

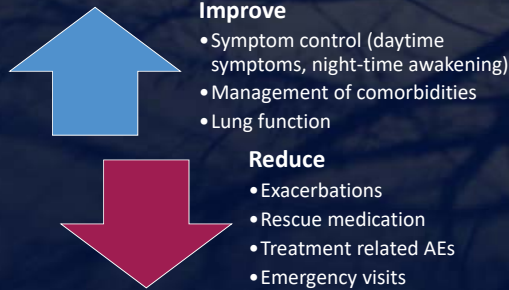
She is using her albuterol several times each day and occasionally waking at night to use it for her coughing. You review her inhaler technique and it is excellent.

**How do you manage this condition?**

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## Goals of Asthma Management

### Reduce Current Impairment and Future Risk

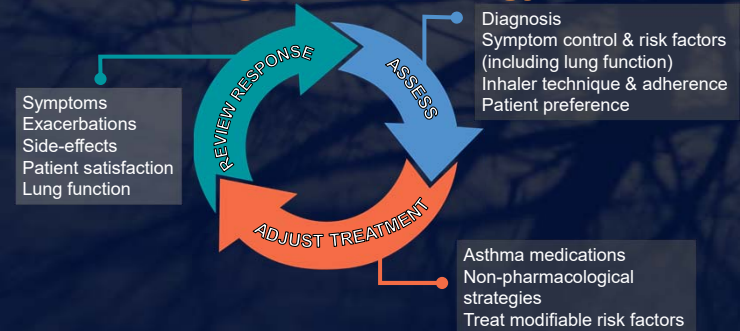


Effective asthma management requires a **partnership** between patient and healthcare provider to define and achieve treatment goals

2018 GINA report, global strategy for asthma management and prevention. <http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed 2018 May 7; NHLBI. NAEPP EPR-3: guidelines for the diagnosis and management of asthma. Full report 2007. <http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report>. Accessed Mar, 2018

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## GINA Recommend a Control-Based Asthma Management Strategy



2018 GINA report, global strategy for asthma management and prevention. <http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed 2018 May 7.

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## Factors that Aggravate Asthma

Comorbidities	Allergen-Based Triggers	Non-Allergic Triggers
<ul style="list-style-type: none"> <li>• Allergic bronchopulmonary aspergillosis</li> <li>• Gastroesophageal reflux</li> <li>• Obesity</li> <li>• Obstructive sleep apnea</li> <li>• Rhinitis/Sinusitis</li> <li>• Stress and depression</li> </ul>	<ul style="list-style-type: none"> <li>• Animal dander</li> <li>• Dust mites</li> <li>• Cockroaches and rodents</li> <li>• Mold and pollens</li> </ul>	<ul style="list-style-type: none"> <li>• Tobacco smoke</li> <li>• Workplace and environmental exposures</li> <li>• Medications                             <ul style="list-style-type: none"> <li>• NSAIDs</li> <li>• Beta-blockers</li> </ul> </li> </ul>

NSAIDs = nonsteroidal anti-inflammatory drugs.  
Slide courtesy of Dennis Williams, PharmD, BCPS, AE-C.

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## Common Aeroallergens



### Diagnostic Testing:

Allergy skin tests  
Blood tests (RAST\*)

\*radioallergosorbent (serum specific IgE test)

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## Modern Therapeutic Paradigm

### Controllers

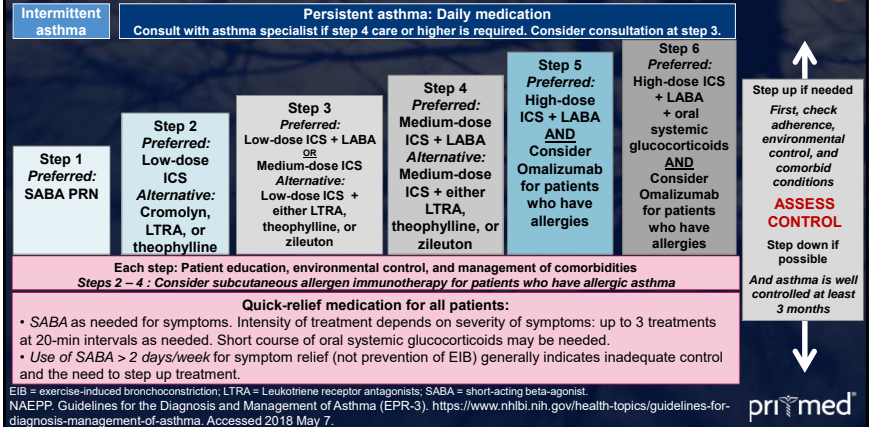
- Inhaled steroids
- Long-acting inhaled bronchodilators
- Leukotriene
- Biologics (anti-IgE, anti-IL-5)

### Quick Relievers

- Quick-acting beta-agonist bronchodilators

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## NAEPP 2007 Guidelines for Asthma



## GINA 2018 Strategy for Asthma Treatment

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
<b>PREFERRED CONTROLLER</b>		Low dose ICS	Low dose ICS/LABA**	Med/high ICS/LABA	Refer for add-on treatment e.g., tiotropium†, anti-IgE, anti-IL5*
<b>Other controller options</b>	Consider low dose ICS	LTRA, Low dose theophylline*	Med/high dose ICS, Low dose ICS+LTRA (or + theoph*)	Add tiotropium†, Med/High dose ICS + LTRA (or + theoph*)	Add low dose OCS
<b>RELIEVER</b>	As-needed SABA		As-needed SABA or low dose ICS/formoterol		

\*Not for children < 12 years; \*\*For children 6 – 11 years, the preferred Step 3 treatment is medium dose ICS; †Add-on treatment for patients with a history of exacerbations. #Low dose ICS/formoterol is the reliever medication for patients prescribed low dose beclomethasone/formoterol maintenance and reliever therapy

2018 GINA report, global strategy for asthma management and prevention. <http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed 2018 May 7.

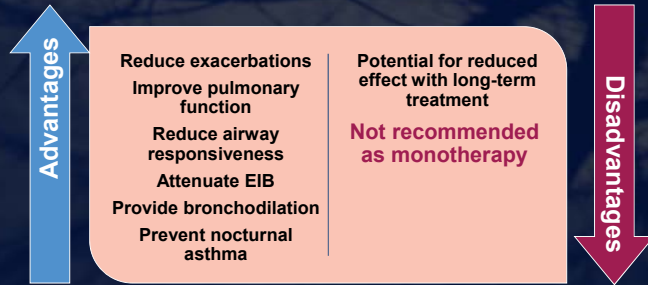
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## Inhaled Corticosteroids First-line Therapy for Persistent Asthma

- ✓ Reduce asthma symptom severity
- ✓ Improve quality of life
- ✓ Improve pulmonary function
- ✓ Reduce rescue inhaler use
- ✓ Reduce exacerbations/ hospitalizations/ ?mortality
- ✓ Reduce bronchial hyperreactivity
- ✓ Slow deterioration of lung function
- ✓ ? May prevent airway remodeling

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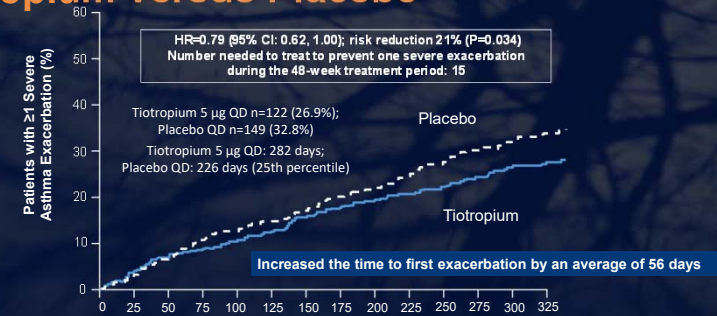
## Long-acting $\beta$ 2-agonists: Salmeterol, Formoterol



Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma Update on Selected Topics 2002. National Asthma Education and Prevention Program. June 2003. NIH Publication No. 02-5074. Available online at <http://www.nhlbi.nih.gov/guidelines/asthma/>.

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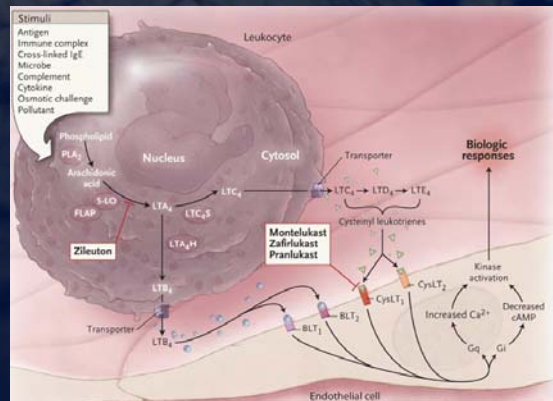
## Risk of Severe Asthma Exacerbation for Tiotropium versus Placebo



Full analysis set. Pooled data. Add-on to high-dose ICS + LABA. Severe exacerbation defined as asthma necessitating the initiation or doubling of systemic corticosteroid therapy for  $\geq 3$  days. CI, confidence interval; HR, hazard ratio. Kerstjens et al. N Engl J Med 2012

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## Leukotriene Modifiers



Peters-Golden M and Henderson W. N Engl J Med 2007;357:1841-1854

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## Choosing Between Controller Options

### Individual Patient Decisions

#### Decisions For Individual Patients

Use shared decision-making with the patient/parent/carer to discuss the following:

1. Preferred treatment for symptom control and risk reduction
2. Patient characteristics (phenotype)
  - Does the patient have any known predictors of risk or response? (e.g. smoker, history of exacerbations, blood eosinophilia)
3. Patient preference
  - What are the patient's goals and concerns for their asthma?
4. Practical issues
  - Inhaler technique – can the patient use the device correctly after training?
  - Adherence: how often is the patient likely to take the medication?
  - Cost: can the patient afford the medication?

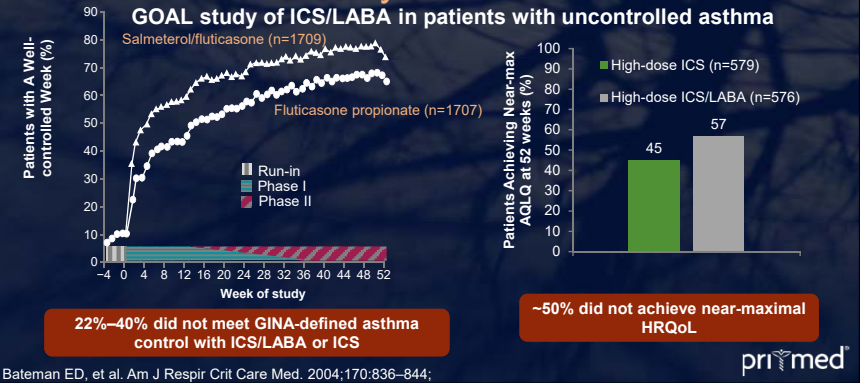
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## Asthma Action Plan General Strategies

- ▶ Use your quick-relief bronchodilator more frequently than usual
- ▶ Increase your dose of inhaled steroids
- ▶ For severe attack, begin or increase dose of oral steroids

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## The Fact: Guideline-Based Asthma Control is not Achieved in Many Patients



## Common Causes of Uncontrolled Asthma That is Not Severe



Nonadherence to therapy<sup>1</sup>

Incorrect inhaler technique<sup>1</sup>

Comorbidities and psychosocial factors<sup>1</sup>

Ongoing exposure to asthma triggers<sup>1</sup>

Understanding a patient's adherence to therapy is always a prerequisite when assessing severe asthma<sup>2</sup>

1. 2018 GINA report, global strategy for asthma management and prevention. <http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed 2018 May 7. 2. Bourdin A et al. Clin Exp Allergy. 2012 Nov;42(11):1566–1574.

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## Non-Adherence is a Significant Problem

Poor adherence

- Common: 50% of adults and children
- Contributes to uncontrolled asthma symptoms/exacerbations

Contributory factors

- Unintentional (e.g., forgetfulness, cost, confusion)
- Intentional (e.g., no perceived need, fear of side-effects, cultural issues, cost)

How to identify patients with low adherence

- Ask an empathic question, e.g., “Do you find it easier to remember your medication in the morning or the evening?” or “Would you say you are taking it 3 days a week, or less, or more?”
- Check prescription date, label date and dose counter
- Ask patient about their beliefs and concerns about the medication

2018 GINA report, global strategy for asthma management and prevention. <http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed 2018 May 7.

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## Proper Inhaler Technique

Poor inhaler technique leads to:

Poor asthma control

Increased risk of exacerbations

Increased adverse effects

- ▶ Up to 70-80% of patients are unable to use their inhaler correctly.
- ▶ Many patients received inadequate education on inhaler technique.
- ▶ Many healthcare providers are unable to demonstrate how to use the inhalers they prescribe.
- ▶ Patients' inhaler technique has been shown to deteriorate over time.
- ▶ Assess proper inhaler technique at multiple visits and prior to concluding that a given therapy is ineffective.

2018 GINA report, global strategy for asthma management and prevention. <http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed 2018 May 7.  
Gagne ME. PLoS One. 2017 Jan 20;12(1):e0170055.

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## General Guidelines for Specialist Referral

- ▶ Life-threatening asthma exacerbation
- ▶ Not meeting treatment goals after 3–6 months\*
- ▶ Atypical presentation/diagnostic difficulties
- ▶ Comorbidities that complicate asthma
  - E.g., sinusitis, nasal polyps, aspergillosis, severe rhinitis
- ▶ Additional diagnostic testing
  - E.g., allergy skin testing, rhinoscopy, provocative challenge
- ▶ Education needed to improve adherence
- ▶ Consideration for immunotherapy
- ▶ Requires step 4 care or higher†
- ▶ > 2 bursts of OCS in 1 year
- ▶ An exacerbation requiring hospitalization
- ▶ Confirmation that an environmental trigger is provoking or contributing to asthma‡

\*An earlier referral or consultation is appropriate if the physician concludes that the patient is unresponsive to therapy; †Consider referral if patient requires step 3 care; ‡Depending on the complexities of diagnosis, treatment, or the intervention required in the environment, it may be appropriate in some cases for the specialist to manage the patient over a period of time or to co-manage with the PCP.  
NAEPP. Guidelines for the Diagnosis and Management of Asthma (EPR-3). [www.nhlbi.nih.gov](http://www.nhlbi.nih.gov). Accessed 9/25/17.

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### Katie Revisited: 30-Year-Old Female

cases

- ▶ Katie is now treated with high-dose ICS in combination with a LABA, together with a leukotriene receptor antagonist (montelukast).
- ▶ However, she continues to complain of frequent exacerbations, and requires multiple courses of oral steroids.
- ▶ You do a complete blood count with differential, which shows eosinophilia (>300 eos/μL)

**What other options are available for her care?**

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## ATS/ERS Definition of Severe Asthma



- ▶ After confirmation of asthma diagnosis and management of comorbidities, severe asthma is defined as:

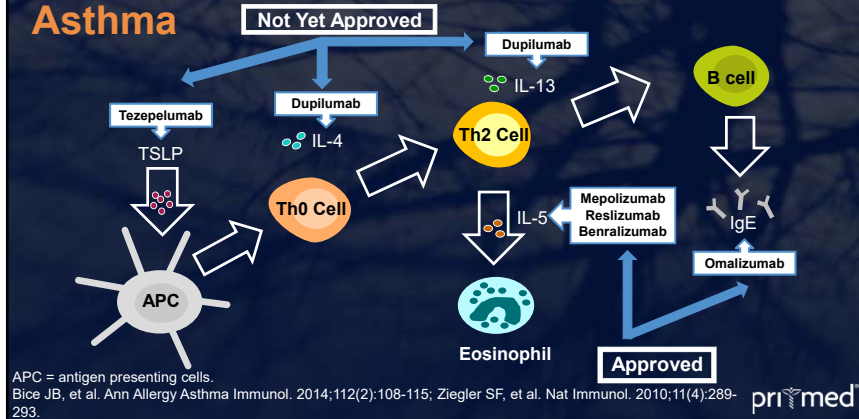
“Asthma which requires treatment with **high dose inhaled corticosteroids (ICS) plus a second controller** (and/or systemic corticosteroids) to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy.”

ATS = American Thoracic Society; ERS = European Respiratory Society.  
Chung KF, et al. Eur Respir J. 2014;43(2):343-373.

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## Novel Therapeutic Targets for Severe Asthma



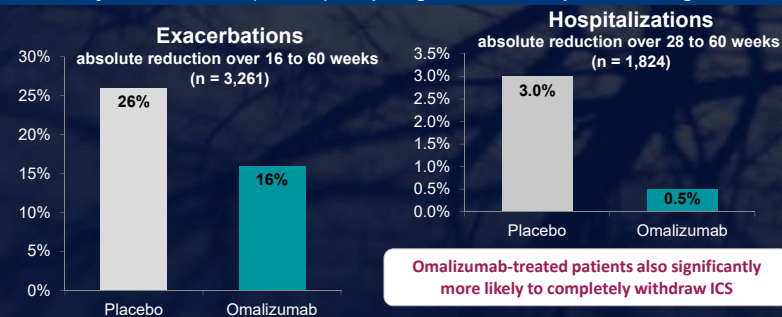
## Anti-IgE Monoclonal Antibody (Omalizumab)

- ▶ Anti-IgE humanized recombinant monoclonal antibody
- ▶ Binds to free circulating IgE at the same site as high-affinity IgE receptor
- ▶ Reduces circulating IgE levels by 95% and leads to a reduction in the number of receptor binding sites on mast cells.
- ▶ Indication: Serum IgE 30-700 IU/ml with sensitivity to >1 perennial allergen
- ▶ AEs: Small risk of delayed anaphylactic reactions
- ▶ Administration: Subcutaneous injection every 2-4 weeks; carry epinephrine pre-filled syringe for 48 hr after injection

Corne et al. J Clin Invest. 1997; 99(5): 879-87.

## Efficacy of Omalizumab in Moderate-to-Severe Allergic Asthma (Cochrane Review)

Meta-analysis of 25 studies (n=6,282) comparing omalizumab to placebo through June 2013



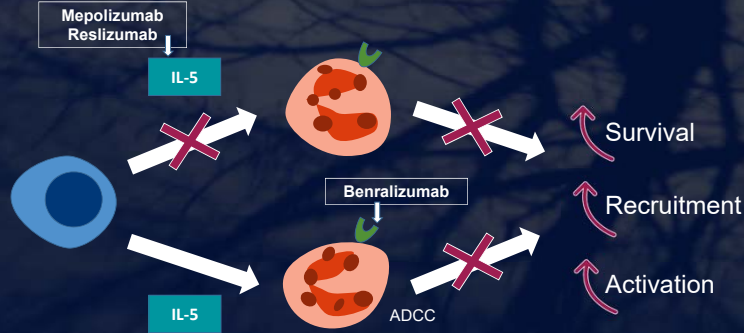
Normansell R. Cochrane Database Syst Rev. 2014 Jan 13;1:CD003559.

## Anti-IL5 Therapy

- ▶ Anti-IL5 monoclonal antibodies (mepolizumab, reslizumab) and Anti-IL5 receptor monoclonal antibody (benralizumab)
- ▶ Reduces asthma exacerbations in patient with eosinophilic asthma and history of exacerbation, and in patients uncontrolled despite high-dose ICS/LABA therapy
- ▶ Indication: Add-on maintenance therapy for patients with severe asthma with an eosinophilic phenotype
- ▶ AEs: Common include benralizumab (headache, pharyngitis); reslizumab (oropharyngeal pain); mepolizumab (headache, injection site rxn, back pain, fatigue)
- ▶ Administration: Subcutaneous injection every 4 weeks

Nixon J et al. Pharmacol Ther. 2017; 169:57-77.

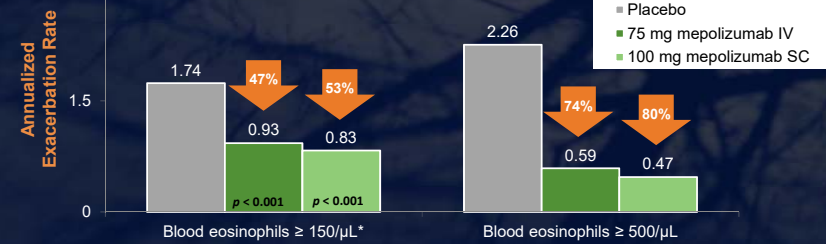
## How Can IL-5 Be Targeted?



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## Efficacy of Mepolizumab in Severe, Eosinophilic Asthma Phase 3 MENSA Trial

576 patients  $\geq 12$  years with severe, eosinophilic asthma received reslizumab add-on therapy to ICS +  $\geq 1$  controller regimen



SIRUS Phase 3 Study (N = 135): mepolizumab demonstrated a **50% OCS dose reduction** (placebo = 0%;  $P = 0.007$ ) while continuing to reduce exacerbations and improve asthma control

\*Eosinophil count  $\geq 150/\mu\text{L}$  at screening or  $\geq 300/\mu\text{L}$  within previous year; \*\*Includes ICS, LABA, tiotropium, and others with the exception of other biologics.

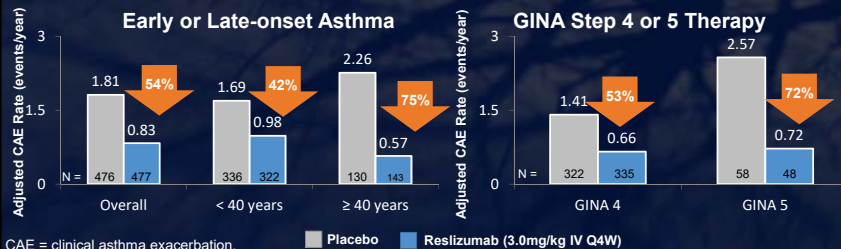
Ortega HG, et al. N Engl J Med. 2014;371(13):1198-1207; Bel EH, et al. N Engl J Med. 2014;371(13):1189-1197.

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## Efficacy of Reslizumab in Patient Subgroups: Post-hoc Analyses

Pooled data from 2 multicenter trials involving 931 patients  $\geq 12$  years with eosinophilic asthma ( $\geq 400$  cells/ $\mu\text{L}$ ) inadequately controlled by medium-to-high dose ICS-based therapy

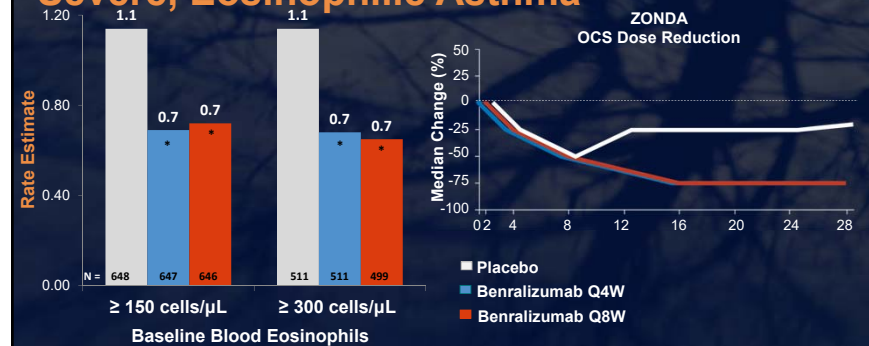
### Clinical Asthma Exacerbation Rate



CAE = clinical asthma exacerbation. Brussels G, et al. Pulm Pharmacol Ther. 2017;43:39-45; Brussels G, et al. ERJ Open Res. 2017;3(3). pii: 00004-2017.

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## Efficacy of Benralizumab in Patients with Severe, Eosinophilic Asthma



\* P value vs. placebo  $< 0.0001$

References: FitzGerald JM, et al. Lancet Respir Med. 2017; Nair P, et al. N Engl J Med. 2017;376(25):2448-2458.

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## Bronchial Thermoplasty



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## Take Home Messages



- ▶ Asthma is a common, complex, and **chronic heterogeneous inflammatory** disease of the airways
- ▶ A diagnosis of asthma is suspected based on history and possibly physical exam and is confirmed by documentation of **variable airflow obstruction** on spirometry
- ▶ In patients on therapy for asthma, assess **asthma control** – based on symptoms, lung function, and frequency of exacerbations
  - ▶ Control is defined as: “well-controlled”, “not well-controlled”, and “very poorly controlled”

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## Take Home Messages



- ▶ In patients with poorly controlled asthma, consider:
  1. Triggers (esp. allergens)
  2. Comorbidities
  3. Medication non-adherence
- ▶ Environmental modification, including reducing allergen exposures, can improve asthma control

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## Take Home Messages



- ▶ **Regular controller therapy** reduces symptoms and decreases exacerbations in patients with persistent symptoms
- ▶ Regularly assess asthma control:
  - ▲ **Step up** therapy in poorly controlled asthma
  - ▼ Maintain or **step down** therapy in well-controlled asthma
- ▶ Successful asthma treatment relies upon medication compliance and **proper inhaler technique**

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## Take Home Messages

- ▶ Differing **endotypes** and **phenotypes** may help explain the variable nature of the disease and help to individualize therapies in difficult-to-control asthma
- ▶ **Novel therapies** exist for severe asthma, targeting elevated IgE, persistent eosinophilia, or smooth muscle hypertrophy
  - ▶ Anti-IgE therapy for severe allergic asthma
  - ▶ Anti-IL5 therapy for severe eosinophilic asthma

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